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Principles of the diuretic using

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ABSTRACT

Water and electrolyte balances are essential in the body. Many conditions, especially heart and kidney failure, venous insufficiency, and drugs, cause edema. In these patients, the diagnosis of edema, the evaluation of the patient in terms of critical underlying pathologies, and appropriate treatment are essential. The use of diuretics in conditions related to the disease is essential for both the treatment of edema and the clinical relief of the patient. Diuretic doses are ineffective or may cause problems due to excessive diuresis when diuretic doses are not appropriately adjusted. This review emphasizes the principles of diuretic use and essential points to be considered.

Keywords: Diuretics, diuretic using, edema

INTRODUCTION

Diuretics consist of large drug families with various mechanisms of action. In general, they are agents that affect a specific target region in the nephron and increase the osmotic pressure in the renal tubule, increasing the excretion of fluid and solute from the kidney or preventing the kidney from holding fluid and solute. However, due to variable efficacy, different side-effect profiles, and secondary benefits of some agents independent of diuretic efficacy, different agents stand out in different diseases (1-3).

DIURETICS

Loop Diuretics

They act by inhibiting the sodium-potassium-chloride cotransporter in the ascending limb of the loop of Henle in the nephron and preventing reabsorption (2,3). Furosemide, torsemide, bumetanide and ethacrynic acid are loop diuretics and the most prominent agent is furosemide (2-4). Furosemide reaches its maximum effect in 1-1.5 hours in oral and 10-30 minutes in intravenous use and has an efficacy of six hours. In kidney failure, the duration of this effect is prolonged, and the potency is reduced. In addition, furosemide is highly bound to blood proteins, and a decrease in furosemide efficacy may be observed in conditions with low albumins, such as nephrotic syndrome. In addition to sodium and fluid excretion, it also causes potassium and calcium loss 3,5,6). Furosemide has found a place for itself in the treatment of acute edema and also in the treatment of hypercalcemia and hyperkalemia with its rapid and robust efficacy. The issues to be considered and avoided in using furosemide are also related to its effectiveness. Furosemide can cause rapid volume depletion with its strong diuretic effect. This can cause hypotension, circulatory and perfusion disorders, and even cardiac collapse. For this reason, its use and dose adjustment should be made with the patient's fluid intake and output monitoring and close monitoring of vital signs, and care should be taken in the presence of hypotension. It can cause calcium-containing kidney stones due to calciuria. It is an ototoxic agent, as it causes hypokalemia, hypomagnesemia, metabolic alkalosis, and hyperuricemia due to its diuretic effect. Lastly, it should be noted that the oral bioavailability of furosemide is in a wide range (10-100%), and the bioavailability decreases with the severity of edema in the gastrointestinal tract (2,3,7). In this patient group, furosemide can be used intravenously, or torsemide, another loop diuretic with a more stable bioavailability of 80-90% and not affected by edema, can be considered as an oral agent. It should be noted that the half-life of torsemide will be prolonged in patients with hepatic dysfunction. Furosemide can slightly lower blood pressure with its vasodilator effect in the first moment, but generally, they do not cause significant hypotension, especially when given by infusion (8,9). The starting dose should be 80 mg in patients with impaired renal function and markedly decreased GFR (3,10). In some patients, the daily dose of furosemide can be increased up to 1500 mg (PO/IV) (11,12).

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Potassium Sparing Diuretics

Spironolactone and eplerenone, known as aldosterone antagonists, act in the cortical collector channel; It reduces sodium absorption and prevents potassium loss. However, this antagonist effect is not limited to the kidney only. As it is known, aldosterone increases as a compensatory mechanism in heart failure and puts the heart into a process of fibrosis and hypertrophy known as remodeling. This mechanism, which makes heart failure sustainable in the short term, is held responsible for mortality in the long term. At this point, spironolactone also competes with aldosterone and slows down this pathological process, and reduces mortality in the long term. As a result, despite the delayed effect and weak effect of aldosterone antagonists, It is a unique and indispensable agent with its mortality-reducing effect in heart failure. In addition, unlike furosemide, it is not affected by low blood albumin and does not need to be secreted from the tubules. Spironolactone, which differs from furosemide in these aspects, should be considered a treatment option in cirrhotic patients where furosemide cannot show its effect. Amiloride and triamterene are other potassium-sparing diuretics that act by directly blocking the epithelial luminal Na channel (ENaC). Their duration of action is much shorter than aldosterone antagonists, and they are particularly prominent in treating Liddle's syndrome. While using potassium-sparing diuretics, the patient should be carefully monitored for the danger of hyperkalemia, and it should be remembered that these drugs may also cause gynecomastia, impotence, or menstrual disorders (2-4,13,14).

Thiazide Diuretics

The thiazide diuretic family exerts its efficacy by inhibiting sodium chloride transport on the distal convoluted tubule in the nephron. Its target site provides natriuresis with a more moderate efficacy profile than loop diuretics. While it provides sodium and chlorine excretion, it restricts calcium excretion. To be effective, it must be secreted into the lumen, and therefore, its effectiveness decreases in patients with eGFR <30 ml/min/1.73m2. In addition, it has a relaxant effect on arteriole smooth muscle, and, in this way, it affects lowering vascular resistance in the periphery (2-4). The prominent member of this family, hydrochlorothiazide, is a diuretic primarily added to the combination treatments against hypertension with all these features. Although it shows its effectiveness within hours when used orally, 1-3 weeks are required for its antihypertensive effectiveness to be seen. Thiazides are primarily used in the treatment of hypertension, as well as in the treatment of hypercalciuria with their calcium-sparing properties. Thiazides can cause hypokalemia, hypercalcemia, hyperlipidemia, hyperglycemia, and hypovolemia (3,4,15,16).

Carbonic Anhydrase Enzyme Inhibitors

Acetazolamide shows diuretic activity by inhibiting sodium hydrogen exchange by inhibiting carbonic anhydrase enzyme in the proximal tubule epithelium. Acetazolamide, which causes bicarbonate accumulation in the lumen, causes alkalosis in the urine and metabolic acidosis in the blood. For this reason, despite its weak diuretic activity, acetazolamide is used as a metabolism stabilizing agent in edematous patients with metabolic alkalosis and chronic lung patients with hypercapnia. In addition, it can be used in cases requiring urinary alkalization and glaucoma. Acetazolamide may cause metabolic acidosis, hypokalemia, and kidney stone formation (1-3,17).

Osmotic Diuretics

Mannitol has a polysaccharide structure and is used as the first choice as an osmotic diuretic. Mannitol is administered intravenously as hypertonic; it is effective by not being reabsorbed in the nephron and keeping the fluid in the compartment with its osmotic effect. When used in high doses or with concomitant renal failure, mannitol may cause volume expansion, hyponatremia, hyperkalemia, and acidosis with an intravenous osmotic diuretic effect. Volume expansion can lead to life-threatening complications such as heart failure or pulmonary edema. Although mannitol provides fluid excretion, it is for these reasons that it finds a place as an emergency treatment option in limited edema tables such as glaucoma and brain edema. During its use, the patient should be closely monitored regarding fluid intake-output balance, electrolytes, kidney functions, and neurological aspects (2,3,18).

New Treatments

Sodium-glucose co-transporter 2 inhibitors: This group includes dapagliflozin and empagliflozin in Turkey. This group of drugs, which are on the market as oral antidiabetic drugs, have revolutionized the treatment of diabetes in terms of blood sugar regulation and weight loss through urinary glucose excretion. With the understanding that they have many benefits in cardiac and renal protection in many studies, they have started to be the most selective treatments, especially in patients in this group with diabetes. In recent studies, significant benefits were found in patients with heart failure and chronic kidney disease without diabetes, and after the results of the studies on patients with heart failure were positive, they were also approved for use in patients with heart failure without diabetes (19-21).

These drugs' most common side effect is urogenital infections, which are frequently seen in women and uncircumcised men. In order to prevent the development of infection, patients should be warned about perineal hygiene. Patients should be warned about genital and

anal hygiene against this complication. In addition, there is a risk of developing euglycemic ketosis, hypoglycemia, and hypotension concerning its mechanism of action. In the presence of chronic kidney disease, renal functions should be monitored. Drugs in this class have not been used when the eGFR is below 30. (22,23).

Angiotensin receptor–neprilysin inhibitor (ARNI): Neprilysin is a neutral endopeptidase and mediates the breakdown of natriuretic peptides, such as adrenomedullin, bradykinin, vasoactive intestinal peptide, and glucagon, by reducing their levels. Although neprilysin is mainly found in the kidney, it is found in many tissues. The purpose of neprilysin inhibition in the treatment of heart failure (HF); is to prevent the decrease in the levels of these substances and to prevent neurohumoral overactivation resulting in water and sodium retention vasoconstriction and inappropriate remodeling due to the decrease of these substances. In addition to increasing fluid and electrolyte balance, a decrease in diuretic therapy requirements has been demonstrated with ARNi treatment; this suggests that ARNi therapy has a diuretic effect potential (24,25). The studies found a relationship between ARN and angioedema, and there was no need for airway compression or endotracheal intubation in patients who developed angioedema. In addition, patients should be monitored for hypotension and hyperkalemia. (26,27)

IMPORTANT POINTS IN THE USE OF DIURETICS

While it can save the life of patients when used in every drug decision (Diuretics are also essential drugs in this respect and can sometimes be life-saving.), insufficient or excessive use of the drug dose can lead to severe life-threatening consequences. Sometimes it can be challenging to adjust the treatment; here, the physician should make the necessary adjustments with his experience and by closely monitoring the patient's response to the treatment. Medicine is an art; there are many gray spots, and each patient's response to treatment is different. Therefore, close follow-up is essential (2-4).

Diuretic therapy should adjust doses according to the patient's renal function (**Table 1**).

Table 1. Diuretic doses according to kidney function

Diuretic	IV loading dose (mg)	Infusion rate (mg/hr) CrCl <25 ml/min	CrCl 25-75 ml/min	CrCl >75 ml/min
Furosemide	40	20-40	10-20	10
Bumetanide	1	1-2	0,5-1	0,5
Torsemide	20	10-20	5-10	5

Adapted from "Brater C. Diuretic therapy. N Engl J Med 1998; 339: 387-395." (3).
CrCl: Creatinine clearance

Chronic diuretic therapy causes many side effects, primarily metabolic; The most common metabolic side effects are given below (**Table 2**) (2-4).

Table 2. Metabolic complications of diuretic therapy

Azotemia (especially in patients with low albumin or very high doses)
Hypokalemia (in 1/3 patients: 0.7-0.8 mEq/L/ mth)
Hyperkalemia*
Gynecomastia*
Hyponatremia
Glucose intolerance / Diabetes mellitus**
Dyslipidemia
Hyperuricemia
Hypomagnesemia
Metabolic alkalosis***
Ototoxicity***

*It is a complication of potassium-sparing diuretic.
**It is a thiazide diuretic complication.
***It is primarily a complication of a loop diuretic.

Considerations in the use of diuretics (2-4-28,29);

- Elderly and people with reduced mobility (significantly obese) may have significant edema in the lower part of the knee despite the lack of excess body volume due to inactivity and sitting all day. In this case, diuretic therapy is not appropriate. The primary treatment should be movement, weight loss, occasional leg elevation, and compression stockings.
- If the patient's albumin level is deficient, water cannot be retained in the vein because the intravascular oncotic pressure is low, and it escapes into the extravascular space and causes edema. Acute renal failure may develop if intense diuretics are given to patients with very low albumin due to edema. Albumin support should be given before or along with it (3).
- Giving diuretics (especially furosemide) in divided doses (or by infusion) is more effective than giving the total dose in one go (3,29).
- The lower the GFR in a patient with renal failure, the less the effect of diuretics (in patients with GFR below 15 ml/min, the amount of loop diuretic secreted tubularly is 1/5-1/10 of that in normal individuals. However, it is absorbed into the lumen. Response to the last diuretic is close to the response kinetics in ordinary people). Therefore, diuretic therapy should be administered at much higher doses than in people with normal renal function (30,31).
- A single dose of IV bolus 160 mg furosemide may cause transient tinnitus with an ototoxic effect; however, if this dose is given as an infusion in 30 minutes instead of a bolus, the risk of tinnitus can be minimized (32).

CONCLUSION

in patients with edema in clinical practice, congestive heart failure, chronic kidney disease, venous insufficiency, drug use causing edema, obesity, etc., situations are increasing and appearing more frequently. Diuretic use is not required in all of these patients. Although there is no edema most of the time, diuretics are used as antihypertensives. Detailed evaluation of the patients, effective diuretic therapy when necessary according to the underlying pathologies, and close follow-up regarding possible side effects and complications are also critical.

ETHICAL DECLARATIONS

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